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«___» _____ 2013

ОТЧЕТ

О НАУЧНО-ИССЛЕДОВАТЕЛЬСКОЙ РАБОТЕ

В рамках выполнения п.2.1.1.1 Плана реализации мероприятий Программы развития УрФУ на 2013 год

ПО ТЕМЕ:

Синтез и химические свойства 3-ацил- и 3-карбэтокси-4-пиронов
(Заключительный)

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Реферат

1. ФИО автора (ов): Обыденнов Дмитрий Львович,

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2. Аннотация:

   По результатам работы опубликовано 2 статьи в реферируемом журнале Tetrahedron Letters и 1 статья в Tetrahedron Letters принята и находится в печати.

Реакция 1-арил-2-диметиламинометиленбутан-1,3-дионов с диэтиоксалатом в присутствии гидрида натрия в ТГФ приводит к образованию этил 5-ароил-4-оксо-4*H*-пиран-2-карбоксилатам, из которых 4-оксо-6-арил-4*H*-пиран-2-карбоновые кислота (6-арилкомановая кислота) были получены с высоким выходом через кислотно катализируемую перегруппировку, сопровождаемую деформилированием. 5-Ароил-4-оксо-4*H*-пиран-2-карбоновые кислоты (5-ароилкомановые кислоты) были синтезированы с помощью последовательности реакций раскрытия/закрытия пиронового цикла обработкой 5-ароил-2-карбэтокси-4-пирона пиперидином с последующим омылением и подкислением.

Аналогично взаимодействие этил 2-диметиламинометилен-3-оксобутаноат с диэтилоксалатом в присутствии гидрида натрия в тетрагидрофуране приводит к диэтил 4-оксо-4*H*-пиран-2,5-дикарбоксилату, из которого 4-оксо-4*H*-пиран-2,5-дикарбоновая и 4-оксо-1-фенил-1,4-дигидропиридин-2,5-дикарбоновая кислоты и их производные с хорошим выходом.

The reaction of 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones with diethyl oxalate in the presence of sodium hydride in THF gave ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates, from which 4-oxo-6-aryl-4*H*-pyran-2-carboxylic acids (6-arylcomanic acids) were obtained in high yields via acid-catalyzed deformylative rearrangement. 5-Aroyl-4-oxo-4*H*-pyran-2-carboxylic acids (5-aroylcomanic acids) were prepared via a ring-opening/ring-closure sequence by the reaction of 5-aroyl-2-carbethoxy-4-pyrones with piperidine and subsequent basic hydrolysis and acidification. And the reaction of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride in THF gave diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate, from which 4-oxo-4*H*-pyran-2,5-dicarboxylic and 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acids and their derivatives were obtained in good yields.

3.

4. Ключевые слова:

   Конденсация Кляйзена, 1-арил-2-(диметиламинометилен)бутан-1,3-дионы; диэтилоксалат; 5-ароил-2-карбэтокси-4-пироны; перегруппировка; 6-арилкомановые кислоты; гидролиз; 5-ароилкомановые кислоты; 4-оксо-4*H*-пиран-2,5-дикарбоновая кислота; 4-оксо-1-фенил-1,4-дигидропиридин-2,5-дикарбоновая кислота

   Claisen condensation; 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones; diethyl oxalate; 5-aroyl-2-carbethoxy-4-pyrones; rearrangement; 6-arylcomanic acids; hydrolysis; 5-aroylcomanic acids; 4-oxo-4*H*-pyran-2,5-dicarboxylic acid; 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acid

5. Тема отчета:

   Синтез и химические свойства 3-ацил- и 3-карбэтокси-4-пиронов.

   Synthesis and chemical properties of 3-acyl- and 3-carbethoxy-4-pyrones.

Synthesis of 6-aryl- and 5-aroylcomanic acids from 5-aroyl-2-carbethoxy-4-pyrones via deformylative rearrangement and ring-opening/ring-closure sequence

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A B S T R A C T

The reaction of 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones with diethyl oxalate in the presence of sodium hydride in THF gave ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates, from which 4-oxo-6-aryl-4*H*-pyran-2-carboxylic acids (6-arylcomanic acids) were obtained in high yields via acid-catalyzed deformylative rearrangement. 5-Aroyl-4-oxo-4*H*-pyran-2-carboxylic acids (5-aroylcomanic acids) were prepared via a ring-opening/ring-closure sequence by the reaction of 5-aroyl-2-carbethoxy-4-pyrones with piperidine and subsequent basic hydrolysis and acidification.

Keywords: Claisen condensation; 1-Aryl-2-(dimethylaminomethylene)butane-1,3-diones; Diethyl oxalate; 5-Aroyl-2-carbethoxy-4-pyrones; Rearrangement; 6-Arylcomanic acids; Hydrolysis; 5-Aroylcomanic acids.

It is known that certain derivatives of 4-oxo-6-phenyl-4*H*-pyran-2-carboxylic acid (6-phenylcomanic acid) selectively inhibit cyclooxygenase-2 enzymes (COX-2) in preference to COX-1, and are useful in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever, and asthma, with fewer side effects.[1] At the same time, these compounds are an important class of γ-pyrones which can serve as the starting materials for the syntheses of a broad range of important heterocycles due to the presence of four electrophilic centers in their molecules (the C-2, C-4 and C-6 atoms of the pyrone system and the carbonyl carbon of the 2-CO_2R group).[2] The diverse range of properties of substituted γ-pyrones is due to the fact that, being highly reactive

enones with a good leaving group at the α- and α′-carbon atoms, whose role is played by the enolate anion, they have the ability to undergo additional transformations related to γ-pyrone ring-opening and heterocyclizations.[3]

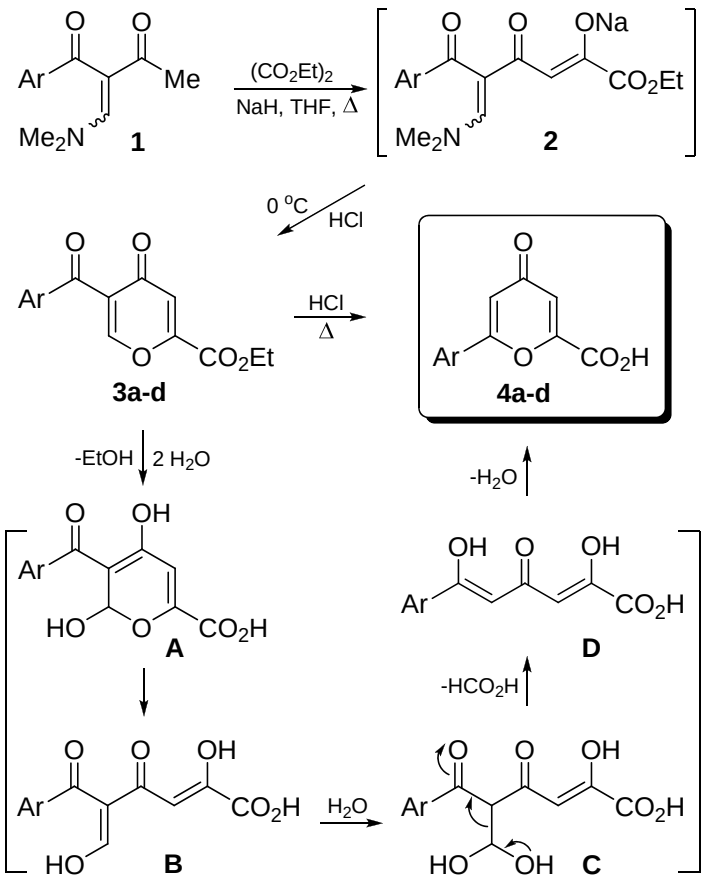
Earlier, 6-phenylcomanic acid was obtained by cyclodehydrobromination of ethyl 5,6-dibromo-2,4-dioxo-6-phenylhexanoate at reflux with KOAc in anhydrous ethanol with subsequent acid hydrolysis of the ethyl 6-phenylcomanate thus formed,[4] as well as by cyclodehydration of 6-phenyl-2,4,6-trioxohexanoic acid, prepared from benzoylacetone and dimethyl oxalate, on heating in acetic acid,[5] and by condensation of 4-phenylbut-3-yn-2-one with diethyl oxalate in the presence of NaOEt.[6] The synthesis of 6-phenylcomanic acid derivatives, with a substituent on the aromatic ring, from the corresponding ethyl 6-aryl-5,6-dibromo-2,4-dioxohexanoates under the action of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[7] and diisopropylamine,[2c] has also been described.

The present communication reports a novel synthesis of 6-arylcomanic acids **4** via acid-catalyzed deformylative rearrangement of ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates **3**. Additionally, the preparation of 5-aroyl-4-pyrone-2-carboxylic acids (5-aroylcomanic acids, **6**) from **3** via a ring-opening/ring-closure sequence is presented. Although the chemistry of comanic acid derivatives has been well documented,[8] compounds **6** are hitherto unreported.

Within the framework of a research program on the synthetic opportunities offered by the γ-pyrone system in the preparation of organic molecules of potential interest in biomedicinal chemistry and materials science,[9] we required large quantities of ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates **3**. To the best of our knowledge, there has only been one report on the preparation of these compounds via the reactions of 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones **1** with diethyl oxalate in the presence of sodium ethoxide in ethanol (no product yields were reported).[10] This is the reason why pyrones **3** belong to a poorly explored class of polycarbonyl compounds, the chemical properties of which have not been investigated.

We found that the Claisen condensation of enaminodiones **1** with diethyl oxalate in the presence of sodium hydride in THF at reflux for eight hours was the method of choice for the preparation of pyrones **3**. After cooling, the reaction mixture was quenched with hydrochloric acid to give 5-aroyl-2-carbethoxy-4-pyrones **3a–d** in 73–82% yields. It turned out that if the hydrolysis of the sodium salts **2** was carried out under milder conditions (4 M HCl, 0 °C, 30 min), the reaction could be stopped at the pyrones **3**, whereas reflux of **3** in dilute HCl (1:1) for eight hours gave 6-arylcomanic acids **4a–d** in 68–85% yields. In the ^{1}H NMR spectra of **3**, protons H-3 and H-6 appeared as singlets at δ 7.23–7.25 and δ 8.13–8.20 ($CDCl_3$), while H-3 and H-5 in **4** appeared as doublets with J = 2.2 Hz at δ 6.98–7.16 and δ 6.84–6.90 (DMSO-d_6), respectively.

A plausible pathway leading to the formation of acids **4** via intermediates **A**–**D** is outlined in Scheme 1. It is clear from this reaction that the ester **3** reacts with water exclusively at its 6-position and in a 1,4-manner, followed by deformylative rearrangement. This transformation represents an alternative route to synthesize acids **4** and makes it possible to obtain these compounds from 1,3-diketones in three steps in 25–60% overall yields. Previously, ethyl 5-chloro- and 5-hydroxy-6-phenyl-4-oxo-4*H*-pyran-2-carboxylates were prepared from epoxypyrones using a similar rearrangement in the presence of formic or perchloric acid.[10a]

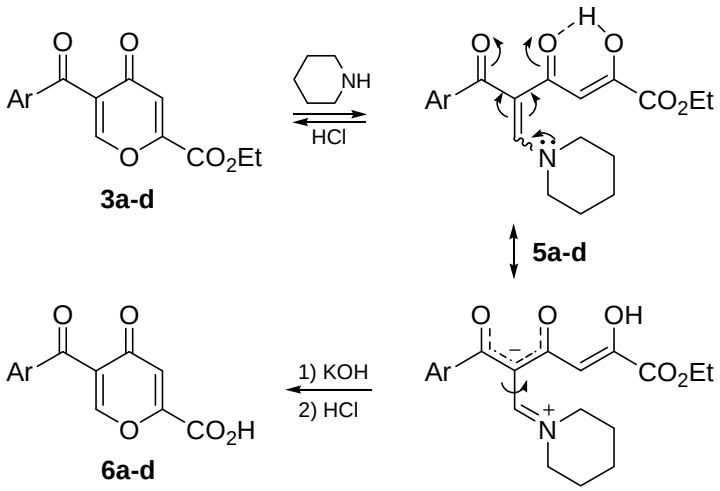


Ar	Pyrone **3**	Yield (%)	Pyrone **4**	Yield (%)
Ph	**3a**	73	**4a**	68
4-$MeOC_6H_4$	**3b**	69	**4b**	72
4-ClC_6H_4	**3c**	82	**4c**	85
2-C_4H_3S	**3d**	73	**4d**	79

Scheme 1. Synthesis of 4-pyrones **3** and **4**.

In connection with this simple rearrangement, the direct hydrolysis of **3** into 5-aroyl-4-pyrone-2-carboxylic acids (5-aroylcomanic acids, **6**) proved impossible, therefore an alternative method for the preparation of compounds **6** was required. We envisaged that the reaction of **3** with piperidine would produce the corresponding enaminotriones **5** bearing a carbethoxy group activated towards nucleophilic attack. In fact, we found that pyrones **3** reacted readily with piperidine in ethanol at 0 °C for one hour to produce enamines **5** in 57–82% yields. This reaction involved attack of the NH group at C-6 of **3** with concomitant opening of the pyrone ring to give compounds **5**, which are reactive polycarbonyl intermediates with an intramolecular hydrogen

bond. The ^{1}H NMR spectra of **5** displayed broad signals for the piperidine function as a result of its only slightly hindered rotation and there was no evidence of two geometric isomers.[11] Treatment of enamines **5** with dilute HCl led to the starting pyrones **3**, however, in line with our expectations, basic hydrolysis of **5** at 0 °C for 15 minutes in the presence of KOH followed by acidification with HCl successfully removed an ethoxy group to give 5-aroylcomanic acids **6** in 61–89% yields[12] as a result of a ring-opening/ring-closure sequence (Scheme 2). Despite their rather simple structures, neither compounds **6** nor their acyclic precursors **5** have previously been prepared. It is pertinent to note that the behavior of compounds **5** closely resembles that already reported by us for 2,5-dicarbethoxy-4-pyrone, which under the same conditions gives 5-carbethoxy-4-pyrone-2-carboxylic acid.[13] Thus, γ-pyrones **3**, due to activation of the conjugated system by two electron-withdrawing groups, are highly electrophilic substrates, which are able to react with *O*- and *N*-nucleophiles, with opening of the pyrone ring.



Ar	Aminoenone **5**	Yield (%)	Pyrone **6**	Yield (%)
Ph	**5a**	82	**6a**	69
4-$MeOC_6H_4$	**5b**	79	**6b**	61
4-ClC_6H_4	**5c**	57	**6c**	89
2-C_4H_3S	**5d**	66	**6d**	80

Scheme 2. Synthesis of compounds **5** and **6**.

In summary, we have developed a novel synthesis of biologically potent 6-arylcomanic acids, which involves the deformylative rearrangement of 5-aroyl-2-carbethoxy-4-pyrones in the

presence of hydrochloric acid. Compared with the previously reported procedures, our method shows several advantages, the main of which are simplicity, efficiency and the ready availability of the starting materials. In addition, 5-aroylcomanic acids were obtained in good yields, for the first time. Taking into account the ability to transform the γ-pyrone system into other compounds, the comanic acid derivatives described here are valuable building blocks for the construction of various heterocyclic systems.

Acknowledgment

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12. *General procedure for the synthesis of compounds* ***3a–d***. A mixture of enaminodione **1** (5.0 mmol), diethyl oxalate (0.88 g, 6.0 mmol) and NaH (60% dispersion in oil, 0.24 g, 6.0 mmol) in THF (15 mL) was refluxed for 8 h. After cooling, the reaction mixture was treated with 4 M HCl until pH = 1, stirred at 0 °C for 30 min, extracted with EtOAc (3 × 15 mL), and evaporated under reduced pressure. The resulting residue was quenched with EtOH to give pyrones **3** as colorless or yellowish crystals.

    General procedure for the synthesis of compounds ***4a–d***. A suspension of the pyrone **3** (1.0 mmol) in dilute HCl (1:1, 2 mL) was stirred at 100 °C for 8 h. The solid that formed was filtered and dried to give pyrones **4** as a white or grey powders.

    *Ethyl 4-oxo-5-(2-thienoyl)-4H-pyran-2-carboxylate (**3d**)*. Yield 73%, mp 97–98 °C, colorless crystals. IR (ATR): 3087, 2983, 2923, 2853, 1728, 1655, 1641, 1621, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H, Me), 4.45 (q, *J* = 7.1 Hz, 2H, CH_2O), 7.14 (dd, *J* = 4.9, 3.9 Hz, 1H, H-4′), 7.24 (s, 1H, H-3), 7.67 (dd, *J* = 3.9, 1.1 Hz, 1H, H-3′), 7.75 (dd, *J* = 4.9, 1.1 Hz, 1H, H-5′), 8.18 (s, 1H, H-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.3, 63.3, 120.2, 129.5, 129.7, 137.4, 137.6, 143.5, 153.3, 157.7, 159.7, 175.6, 182.5. Anal. Calcd for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62. Found: C, 56.02; H, 3.53.

    *4-Oxo-6-(2-thienyl)-4H-pyran-2-carboxylic acid (**4d**)*. Yield 79%, grey powder, mp 252–253 °C. IR (ATR): 3108, 3085, 1730, 1623, 1594, 1573 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, *J* = 2.3 Hz, 1H, H-5), 6.98 (d, *J* = 2.3 Hz, 1H, H-3), 7.27 (dd, *J* = 5.0, 3.9 Hz, 1H, H-4′), 7.93 (dd, 1H, *J* = 3.9, 1.1 Hz, H-3′), 7.95 (dd, 1H, *J* = 5.0, 1.1 Hz, H-5′), 12.0–15.5 (br s, 1H, OH); ^{13}C NMR (100

MHz, DMSO-d_6): δ 110.6, 118.4, 129.4, 129.9, 132.4, 133.7, 153.2, 159.5, 161.3, 178.8. Anal. Calcd for $C_{10}H_6O_4S$: C, 54.05; H, 2.72. Found: C, 54.03; H, 2.75.

*Ethyl 2-hydroxy-4-oxo-6-(piperidin-1-yl)-5-(2-thienoyl)hexa-2,5-dienoate (**5d**)*. Yield 66%, yellow powder, mp 125–126 °C. IR (ATR): 3131, 3069, 2998, 2984, 2951, 1725, 1604, 1586 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, J = 7.1 Hz, 3H, Me), 1.35–1.70 (br s, 6H, $3CH_2$), 2.9–3.8 (br s, 4H, $(CH_2)_2N$), 4.19 (q, J = 7.1 Hz, 2H, CH_2O), 6.29 (s, 1H, =CH), 7.21 (dd, J = 4.9, 3.9 Hz, 1H, H-4′), 7.65 (dd, J = 3.9, 1.2 Hz, 1H, H-3′), 8.03 (dd, J = 4.9, 1.2 Hz, 1H, H-5′), 8.06 (s, 1H, =CHN), 15.0–16.5 (br s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 22.8, 22.9, 44.3, 61.9, 100.0, 107.0, 129.3, 134.6, 136.2, 146.4, 154.7, 161.9, 163.0, 187.6, 188.6. Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.45; H, 5.72, N, 3.72.

*4-Oxo-5-(2-thienoyl)-4H-pyran-2-carboxylic acid (**6d**)*. Yield 80%, yellowish powder, mp 218–220 °C. IR (ATR): 3452, 3097, 1727, 1651, 1627 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ^1H NMR (400 MHz, DMSO-d_6) δ 7.02 (s, 1H, H-3), 7.26 (dd, J = 4.8, 4.0 Hz, 1H, H-4′), 7.83 (dd, J = 4.0, 1.2 Hz, 1H, H-3′), 8.15 (dd, J = 4.8, 1.2 Hz, 1H, H-5′), 8.71 (s, 1H, H-6) (the OH proton was not observed due to broadening); ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.9, 129.5, 129.6, 137.4, 137.5, 143.5, 154.4, 157.8, 161.1, 175.9, 182.7. Anal. Calcd for $C_{11}H_6O_5S \cdot H_2O$: C, 49.25; H, 3.01. Found: C, 49.51; H, 2.98.

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An improved synthesis and some reactions of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate

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ABSTRACT

The reaction of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride in THF gave diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate, from which 4-oxo-4*H*-pyran-2,5-dicarboxylic and 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acids and their derivatives were obtained in good yields.

Chelidonic acid, a γ-pyrone compound with the structure shown in Figure 1, is a naturally occurring compound that is widely distributed among many plants.[1] It is contained in the rhizomes of *Chelidonium majus* L. at quite high concentrations, and has multiple pharmacological effects including mild analgesic, antimicrobial, oncostatic, and central nervous system sedation.[2] In addition, chelidonic acid and chelidamic acid were the most potent inhibitors of glutamate decarboxylase from rat brain,[3] and may attenuate allergic reactions by inhibition of caspase-1 activity.[4]

Unlike well-studied diethyl chelidonate,[5] diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (diethyl isochelidonate), is much less known. Furthermore, none of the isomeric 4-pyrone dicarboxylic acids **I**–**III** has been recorded in the literature (Fig. 1). Diethyl isochelidonate was mentioned for the first time in 2012 in the patent literature,[6] as a novel intermediate for synthesizing an anti-influenza drug exhibiting cap-dependent endonuclease inhibitory activity.

γ-Pyrone derivatives bearing electron-withdrawing carbonyl-containing substituents at the 2- and 5-positions have, surprisingly, been poorly investigated, probably due to the limited number of methods available for their preparation.[6,7] At the same time, these compounds are an important class of γ-pyrones which can serve as the starting materials for the syntheses of a broad range of heterocyclic systems due to the presence of five electrophilic centers in their molecules (the C-2, C-4 and C-6 atoms of the pyrone system, and the carbonyl carbons of the 2-COR and 5-COR′ groups). The diverse range of properties of these compounds is due to the fact that, being highly reactive geminally activated push–pull alkenes with a good leaving group at the α- and α′-carbon atoms, whose role is played by the enolate anion, they acquire the ability to undergo additional transformations related to γ-pyrone ring-opening and heterocyclizations.

The present Letter describes an improved synthesis of diethyl isochelidonate (**1**), which consists of the Claisen condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride. Moreover, the synthesis

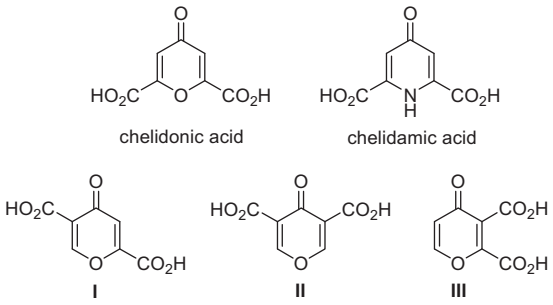

Figure 1. Some natural and unnatural γ-pyrone dicarboxylic acids.

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of 4-pyrone-2,5-dicarboxylic acid [isochelidonic acid (**2**)] and its derivatives, including *N*-phenylisochelidamic acid, is presented. Although the chemistry of 4-pyrones and 4-pyridones has been well documented,[8] isochelidonic and isochelidamic acids are hitherto unreported.

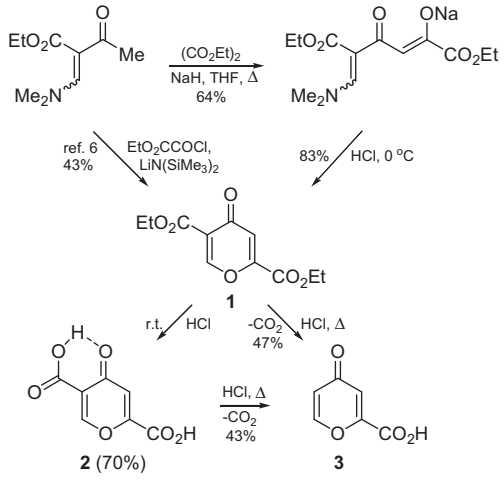
Within the framework of a research program on the synthetic opportunities offered by the γ-pyrone system in the preparation of organic molecules having potential interest in biomedicinal chemistry and materials science,[9] we had a requirement for large quantities of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (**1**). To the best of our knowledge, there has only been one report on the preparation of diester **1** via the reaction of ethyl 2-(dimethylamino)methylene-3-oxobutanoate, prepared from ethyl acetoacetate and dimethylformamide dimethyl acetal,[10] with ethyl oxalyl chloride in the presence of hexamethyldisilazane in THF at −78 °C.[6] However, on repeating this procedure, we were unable to obtain **1** in a reasonable yield. Instead, we found that the Claisen condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride in THF at reflux for 5 h was the method of choice for the preparation of isochelidonic ester **1**. After cooling, the intermediate sodium salt was filtered, washed with THF (yield 64%), dissolved in water, and quenched with concentrated HCl to give diester **1** in 83% yield (overall yield 53%). Note that **1** could be prepared without isolation of the sodium salt, however, a higher yield and easier purification of compound **1** were possible if the reaction was performed in a two-step approach. Unlike the previously reported method,[6] this reaction did not require a low temperature or any chromatographic purification of the final product, and thereby greatly facilitated the preparation of the target diester **1**[11] (Scheme 1).

As mentioned above, γ-pyrone-2,5-dicarboxylates belong to a poorly explored class of polycarbonyl compounds, the chemical properties of which have not been investigated. In connection with this, we examined the reactivity of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (**1**) in order to obtain potentially biologically interesting derivatives. We found that if the hydrolysis of diester **1** was carried out under milder conditions (conc. HCl, ~20 °C, 3 days), the reaction could be stopped at the diacid **2** (yield 70%),[12] whereas reflux of **1** in dilute HCl (1:1) for 7 h gave comanic acid (**3**) in 47% yield, which could also be obtained by decarboxylation of isochelidonic acid (**2**) under the same conditions (43% yield). These reactions represent an alternative route to synthesize comanic acid (**3**). Our approach makes it possible to obtain this compound from acetoacetic ester in three steps (overall yield 25%), whereas the method described in the literature[13] for the synthesis of comanic acid (**3**) consists of five steps and starts from acetone and diethyl oxalate via an acetonedioxalic ester (overall yield 33%).

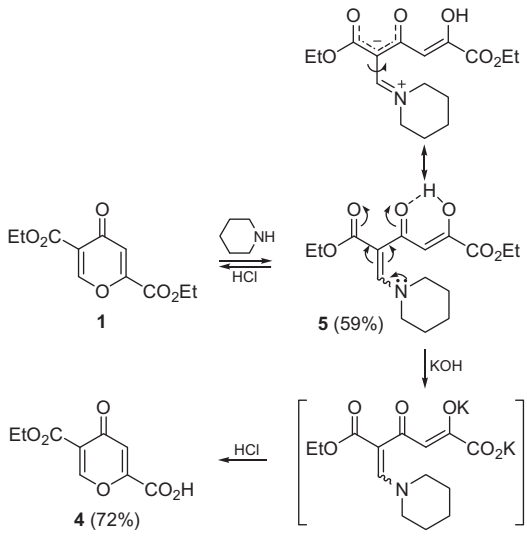
There is no significant difference in the chemical reactivity of the 2- and 5-carbethoxy groups, and all our attempts to obtain the monoester starting from diester **1** were unsuccessful. Thus, an alternative method for the preparation of 5-carbethoxy-4-pyrone-2-carboxylic acid (**4**) was developed. We envisaged that the reaction of **1** with piperidine would produce the corresponding enaminone **5** with one deactivated carbethoxy group, the slow reaction of which with water could be connected with the presence of the electron-donating piperidine moiety. The second carbethoxy group of the compound **5** will be activated toward nucleophilic attack by the adjacent carbonyl group. In fact, we found that diethyl isochelidonate (**1**) reacted readily with piperidine in ethanol at 0 °C for two hours and then at −20 °C over two days to produce compound **5** in 59% yield. This reaction involved attack of the NH group at C-6 of **1** with concomitant opening of the pyrone ring to give **5**, which is a reactive polyfunctionalized intermediate with an intramolecular hydrogen bond. The ^{1}H NMR spectrum of **5** displayed broad signals for the piperidine function as a result of its only slightly hindered rotation and there was no evidence of two geometric isomers.[10] Treatment of amino-enone **5** with dilute HCl led to the starting pyrone **1**, however, in line with our expectations, basic hydrolysis of compound **5** at 0 °C for 15 min followed by acidification successfully removed only one ethoxy group to give monoethyl isochelidonate (**4**) in 72% yield[14] (Scheme 2).

The structures of pyrones **2** and **4** were established from their elemental analyses and spectral (^{1}H, ^{13}C NMR, and IR) data. In their ^{1}H NMR spectra, protons H-3 and H-6 appeared as singlets at δ 6.94–7.09 and δ 8.86–9.00, respectively, in the ^{13}C NMR spectra, the pyrone carbonyls appeared at δ 174.5 for monoester **4** and δ 177.5 for diacid **2** (it is well-known[15] that intramolecular hydrogen bonding causes substantial downfield shifts).

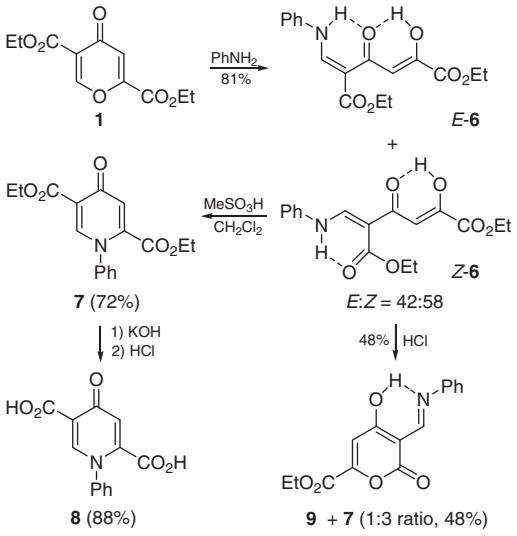
Thus, γ-pyrone **1**, due to activation of the conjugated system by two electron-withdrawing carbethoxy groups, is a highly electrophilic substrate, which is able to react with *O*- and *N*-nucleophiles, with or without affecting the pyrone ring. During the preparation of the isochelidamic acid derivatives, it was also found that treatment of **1** with aniline at 0 °C for 30 min gave amino-enone **6** as a 42:58 mixture of *E*- and *Z*-isomers in 81% yield. It is clear that the diester **1** reacts with aniline exclusively at its 6-position and in a 1,4-manner. The main information for the characterization of this mixture was obtained from the ^{1}H NMR spectrum in $CDCl_3$, which showed two



Scheme 1. Synthesis of compounds **1**–**3**.



Scheme 2. Synthesis of monoester **4**.



Scheme 3. Synthesis of compounds **6**–**9**.

sets of signals. The most downfield shifted signals at δ 15.77 (s, OH), 11.37 (d, J = 14.2 Hz, NH), 8.79 (d, J = 14.2 Hz, =CHN), 7.34 (s, =CH) and at δ 14.55 (s, OH), 12.53 (d, J = 13.5 Hz, NH), 8.63 (d, J = 13.5 Hz, =CHN), 7.61 (s, =CH) were assigned tentatively to isomers *Z*-**6** and *E*-**6**, respectively. These data indicate that both labile protons are involved in the formation of strong intramolecular hydrogen bonds, thus confirming the structure of **6**.

In comparison to the reaction with piperidine, the use of methanesulfonic acid in dichloromethane at room temperature for three hours transformed amino-enone **6** irreversibly into diethyl *N*-phenylisochelidamate (**7**) in 72% yield.[16] Basic hydrolysis of **7** proceeded in the expected manner to give *N*-phenylisochelidamic acid (**8**) (yield 88%),[17] which may be of interest as a biologically valuable compound.[6] Despite their rather simple structures, neither compound **7** nor its parent acid **8** has been prepared previously; from this series of compounds only 5-carbethoxy-4-oxo-1,4-dihydropyridine-2-carboxylic acid was known.[18] Treatment of amino-enone **6** with a catalytic amount of concentrated HCl in ethanol at room temperature for 12 h gave a mixture of compounds **9** and **7** in the ratio of 1:3 (yield 48%) (Scheme 3).

In summary, we have developed an improved synthesis of biologically potent diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate, which involves the condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride. Compared with the previously reported procedure, our method shows several advantages, the main of which are simplicity, efficiency, and the ready availability of the starting materials. From this diester, for the first time, isochelidonic acid and its derivatives have been obtained in good yields. Taking into account the ability to transform an ester group into other functional groups, the 4-pyrone-2,5-dicarboxylate core is a valuable building block for the construction of a wide range of 4-pyrone derivatives.

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11. *Sodium (5E)-6-(dimethylamino)-1-ethoxy-5-(ethoxycarbonyl)-1,4-dioxohexa-2,5-dien-2-olate:* A mixture of ethyl 2-(dimethylamino)methylene-3-oxobutanoate (3.0 g, 16.2 mmol), diethyl oxalate (2.84 g, 17.3 mmol), and NaH (60% dispersion in oil) (0.84 g, 21.0 mmol) in THF (45 mL) was refluxed for 5 h. After cooling, the solid that formed was filtered, washed with THF (10 mL), and dried. Yield 3.22 g (64%), mp 220 °C (dec.), beige powder. IR (ATR): 2982, 1709, 1689, 1663, 1571 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (br t, J = 7.0 Hz, 3H, Me), 1.20 (t, J = 7.0 Hz, 3H, Me), 2.88 (s, 6H, NMe_2), 3.97 (br q, J = 7.0 Hz, 2H, CH_2O), 4.05 (q, J = 7.0 Hz, 2H, CH2O), 5.65 (s, 1H, =CH), 7.14 (br s, 1H, =CHN). *Diethyl 4-oxo-4H-pyran-2,5-dicarboxylate (**1**):* Sodium (5*E*)-6-(dimethylamino)-1-ethoxy-5-(ethoxycarbonyl)-1,4-dioxohexa-2,5-dien-2-olate (3.0 g, 9.76 mmol) was dissolved in H_2O (10 mL) and quenched with concentrated HCl (3 mL) at 0 °C (ice bath) for 30 min. The product **1** was extracted with EtOAc (3 × 7 mL) and recrystallized from hexane with the addition of small amounts of toluene. Yield 1.94 g (83%), mp 71–72 °C (in Ref.[6] described as an oil), beige powder. IR (ATR): 3051, 2988, 1751, 1727, 1652, 1572 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H, Me), 1.37 (t, J = 7.1 Hz, 3H, Me), 4.34 (q, J = 7.1 Hz, 2H, CH_2O), 4.41 (q, J = 7.2 Hz, 2H, CH_2O), 7.18 (s, 1H, H-3), 8.53 (s, 1H, H-6).
12. *4-Oxo-4H-pyran-2,5-dicarboxylic acid (isochelidonic acid) (**2**):* A solution of diester **1** (0.20 g, 0.83 mmol) in concentrated HCl (2 mL) was stirred for 3 d at room temperature. The resulting solid was filtered, washed with H_2O, and then toluene. Yield 0.117 g (70%), mp 288–290 °C (dec.), beige powder. IR (ATR): 3530, 3428, 3084, 1751, 1713, 1662, 1605, 1560 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (s, 1H, H-3), 9.00 (s, 1H, H-6), 11.0–15.0 (br s, 2H, 2OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 119.9, 120.4, 154.8, 160.7, 163.0, 163.7, 177.5. Anal. Calcd for $C_7H_4O_6{\cdot}H_2O$: C, 41.60; H, 2.99. Found: C, 41.66; H, 2.75.
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14. *5-(Ethoxycarbonyl)-4-oxo-4H-pyran-2-carboxylic acid (**4**):*A mixture of amino-enone **5** (120 mg, 0.37 mmol) and KOH (103 mg, 1.83 mmol) in H_2O (2 mL) was

stirred for 15 min at 0 °C and quenched with 4 M HCl until pH 1. The resulting solid was separated by filtering and washed with cold H_2O. Yield 56 mg (72%), mp 238–240 °C, white powder. IR (ATR): 3071, 3006, 1729, 1641, 1592, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.27 (q, J = 7.1 Hz, 3H, Me), 4.24 (q, J = 7.1 Hz, 2H, CH_2O), 6.94 (s, 1H, H-3), 8.86 (s, 1H, H-6) (the OH proton was not observed due to broadening); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.5, 61.4, 120.5, 121.7, 153.8, 161.0, 161.9, 162.6, 174.5. Anal. Calcd for $C_9H_8O_6$: C, 50.95; H, 3.80. Found: C, 51.07; H, 3.54.

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16. *Diethyl 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylate (**7**):* A solution of amino-enone **6** (200 mg, 0.60 mmol) and $MeSO_3H$ (115 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was stirred for 3 h. The solvent was removed and the residue was diluted with H_2O. The solid that formed was filtered and recrystallized from hexane–toluene (4:1). Yield 147 mg (72%), mp 141–142 °C, colorless crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 3H, Me), 1.37 (t, J = 7.1 Hz, 3H, Me), 4.11 (q, J = 7.1 Hz, 2H, CH_2O), 4.37 (q, J = 7.1 Hz, 2H, CH_2O), 7.06 (s, 1H, H-3), 7.28–7.32 (m, 2H, Ph), 7.50–7.54 (m, 3H, Ph), 8.27 (s, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.2, 61.2, 62.6, 119.5, 124.9, 125.1, 129.5, 129.8, 140.3, 142.2, 148.1, 161.3, 164.2, 174.8. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.58; H, 5.32; N, 4.27.
17. *4-Oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acid (**8**):* To a suspension of diester **7** (100 mg, 0.32 mmol) in H_2O (2 mL) was added KOH (107 mg, 1.90 mmol) and the mixture was stirred at room temperature (30 min) and then at reflux (30 min). After cooling, the mixture was quenched with 4 M HCl until pH 1, and the solid that formed was filtered and washed with H_2O. Yield 72 mg (88%), mp 223-224 °C, colorless powder. ^1H NMR (400 MHz, DMSO-d_6) δ 7.15 (s, 1H, H-3), 7.52–7.58 (m, 5H, Ph), 8.49 (s, 1H, H-6) (the OH protons were not observed due to broadening). Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 60.10; H, 3.29; N, 5.45.
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A novel, two-step synthesis of 4-pyridone-3-carboxamides from 2-cyano-4-pyrones

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Cyclization

ABSTRACT

Reactions of 2-cyano-6-(trifluoromethyl)-4-pyrone, 2-cyano-4-pyrone, and 2-cyano-6-methyl-4-pyrone with aliphatic and aromatic amines in ethanol at −20 °C for 2–21 days gave 5-amino-3-oxopent-4-enamides in 28–78% yields, which were cyclized with DMF-DMA in toluene under ambient conditions to afford 4-pyridone-3-carboxamides in 31–70% yields.

4-Pyridone-3-carboxamides belong to an important class of nitrogen-containing heterocyclic compounds with a broad spectrum of biological activities. Many of their derivatives are selective CB2 cannabinoid receptor ligands,[1] and possess herbicidal[2] and anti-inflammatory[3] activities. These heterocyclic amides also exhibit properties of plant growth regulators[4] and are the key frameworks of some natural products (e.g., aspernigrine A and pestalamides B and C[5]) (Fig. 1).

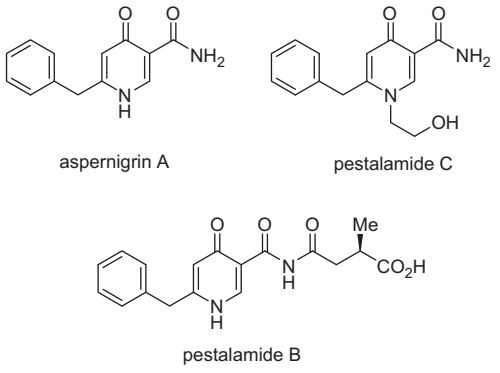

Figure 1. Examples of natural compounds containing a 4-pyridone-3-carboxamide framework.

Reported synthetic methods for the preparation of 4-pyridone-3-carboxamides are based on the reactions of 4-pyrone-3-carboxylic acid derivatives with amines (transformation of the 4-pyrone ring into a 4-pyridone ring),[1,4] the treatment of α-acylated enaminoamides with *N*,*N*-dimethylamide dimethyl acetals,[4b,c] the reaction of 3-aminoacrylic acid derivatives with 2,2,6-trimethyl-1,3-dioxin-4-one[4] or diketene,[3] the transformation of 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) into 4-pyridone-3-carboxylic acid derivatives,[1] as well as the self-condensation of *N*-aryl acetoacetamides mediated by sodium persulfate[5b] or *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water.[3] In this Letter, we report a novel synthesis of 4-pyridone-3-carboxamides from 5-amino-3-oxopent-4-enamides, which in turn were prepared from the corresponding 2-cyano-4-pyrones.

We previously found[6] that dehydration of 4-*oxo*-6-(trifluoromethyl)-4*H*-pyran-2-carboxamide (**1a**)[7] with trifluoroacetic anhydride in the presence of pyridine at 0 °C led to the formation of 2-cyano-6-(trifluoromethyl)-4-pyrone (**2a**) in 61% yield. We now report the synthesis of 2-cyano-4-pyrone (**2b**) and 2-cyano-6-methyl-4-pyrone (**2c**) from the corresponding 4-pyrone-2-carboxamides **1b**,**c** under the same conditions, in 48%[8] and 55% yields, respectively (it proved important to carry out the reaction at −10 °C). Surprisingly, as in the case of **1a** and **2a**, the isolation and characterization of which had not been reported prior to our work,[6,7] none of these simple 2-cyano- and 2-carbamoyl-4-pyrones had been recorded in the literature (Scheme 1).

Pyrone **2a**, due to activation of the conjugated system by two electron-withdrawing groups (CF_3 and CN), is a highly electrophilic

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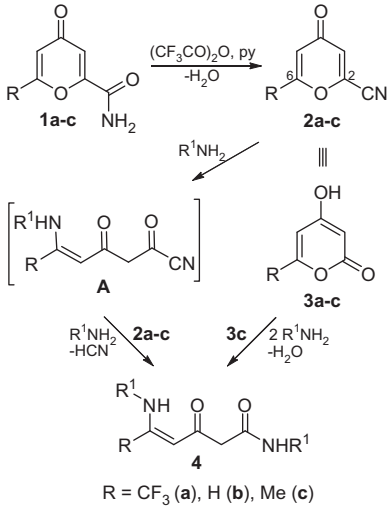


Scheme 1. Synthesis of 5-amino-3-oxopent-4-enamides **4**.

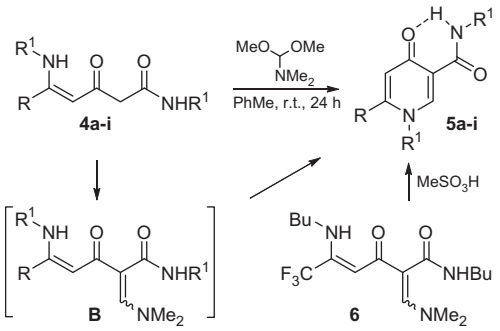
substrate, which is able to react with different nucleophiles with or without affecting the pyrone ring.[6] We found that **2a** reacted easily with both aliphatic and aromatic amines in ethanol at −20 °C over 2 days to produce CF_3-containing 5-amino-3-oxopent-4-enamides **4a**–**f** in yields of 28–78%. The first step of the reaction leading to **4** presumably involves attack of the NH_2 group at C-6 of **2a** with concomitant opening of the pyrone ring to give intermediate **A**, which is a reactive acyl cyanide. Subsequent substitution of the cyano group adjacent to the carbonyl group occurs by the action of a second amine molecule and leads to the carbamoylated aminoenones **4**. This reaction reveals the high reactivity of the pyrone ring of **2a** in contrast to the pyrone ring of 2-cyano-4-pyrone (**2b**), which reacted with benzylamine and *p*-anisidine at −20 °C over 8 days to give aminoenones **4g**,**h** in good yields (49–62%). The less reactive 2-cyano-6-methyl-4-pyrone (**2c**) reacted under the same conditions only with benzylamine, over 3 weeks, to produce compound **4i** in 50% yield, which has been previously obtained from triacetic acid lactone (**3c**) and benzylamine[9] (Scheme 1 and Table 1). Thus, 2-cyano-4-pyrones **2** can be considered as synthetic equivalents of 4-hydroxy-2-pyrones **3**, of which 4-hydroxy-6-(trifluoromethyl)-2-pyrone (**3a**) and 4-hydroxy-6-methyl-2-pyrone (**3c**) are known compounds.[10]

5-Amino-3-*oxo*-4-enamides **4** belong to a poorly explored class of polyfunctional compounds, the chemical properties of which have still not been investigated (besides acid hydrolysis to 4-hydroxy-2-pyridones[6,9]). In connection with this, we examined the reactivity of carbamoylated aminoenones **4** to construct biologically interesting CF_3-containing 4-pyridone-3-carboxamides as well as non-fluorinated pyridones. We reasoned that reaction of

Table 1
Yields and melting points of amides **4** and pyridones **5**

R	R^1	Amide	Yield (%)	mp (°C)	Pyridone	Yield (%)	mp (°C)
CF_3	Me	**4a**	37	104–105	**5a**	64	175–176
CF_3	Ph	**4b**	78	108–109	**5b**	60	161–162
CF_3	2-$MeOC_6H_4$	**4c**	59	119–120	**5c**	62	212–213
CF_3	4-$MeOC_6H_4$	**4d**	58	131–132	**5d**	68	182–183
CF_3	4-BrC_6H_4	**4e**	28	187–188	**5e**	31	241–242
CF_3	*n*-Bu	**4f**	76	65–66	**5f**	56[a]	liq.
H	$PhCH_2$	**4g**	62	113–114	**5g**	54	129–130
H	4-$MeOC_6H_4$	**4h**	49	152–153	**5h**	70	201–202
Me	$PhCH_2$	**4i**	50	107–108[b]	**5i**	58	163–164

[a] From **6**.
[b] mp 106–108 °C (Ref.13).



Scheme 2. Synthesis of 4-pyridone-3-carboxamides **5**.

DMF-DMA with an appropriately substituted amide **4** would provide the desired 4-pyridones. During the optimization studies, it was found that treatment of compounds **4a**–**i** with DMF-DMA in toluene under ambient conditions for 24 h gave 4-pyridone-3-carboxamides **5a**–**i** in 31–70% yields.[11,12] The mechanism of the reaction involves α-enamination of **4** with DMF-DMA to give intermediate **B**, which then undergoes cyclization to afford 4-pyridone-3-carboxamides **5**. Indeed, in the case of *N*,*N*′-dibutyl substituted amide **4f**, intermediate acyclic product **6** was isolated as a single isomer in 65% yield. The latter was converted into the corresponding 4-pyridone **5f** by treatment with methanesulfonic acid in toluene at room temperature over 0.5 h (Scheme 2 and Table 1).

Although the chemistry of 4-pyridones has been well documented,[1–5] compounds **5** are hitherto unreported. This new cyclization process allows the preparation of a variety of 4-pyridone-3-carboxamides **5** with substituents on the amide and ring nitrogen atoms, and proves that the methylene component of the β-ketoamide moiety is more reactive to DMF-DMA than the methylene component of the aminoenone moiety.

The structures of all the compounds were established from their elemental analyses and spectral (^1H, ^{13}C NMR, and IR) data. In the ^1H NMR spectra of pyridones **5**, protons H-2 and H-5 appeared as superfluous 0 singlets at δ 8.37–8.67 and δ 5.63–7.26, respectively (doublets for **5g**,**h**, ^3J = 7.4 Hz, ^4J = 2.2 Hz). Another characteristic feature was the appearance of the NH signal in the range of δ 9.8–12.5, indicating that there is intramolecular hydrogen bonding in **5**.[3] In the ^{13}C NMR spectrum of **5d**, three characteristic quartets due to the CF_3 (δ 119.3, $^1J_{C,F}$ = 275.0 Hz), C-5 (δ 119.9, $^3J_{C,F}$ = 4.2 Hz), and C-6 (δ 138.2, $^2J_{C,F}$ = 33.5 Hz) carbons were observed, additionally confirming the 4-pyridone structure.

In summary, we have developed a simple two-step synthesis of potentially biologically active 4-pyridone-3-carboxamides, including CF_3-containing derivatives, which involves the preparation of 5-amino-3-oxopent-4-enamides via the reaction of 2-cyano-4-pyrones with amines, and their subsequent cyclization under the action of DMF-DMA.

Acknowledgment

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8. *2-Cyano-4-pyrone (**2b**).* Yield 50 mg (48%), yellowish crystals, mp 89–90 °C (toluene). IR (ATR) 1705, 1621, 1599, 1502, 1483, 1474 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.53 (1H, dd, J = 6.0, 2.6 Hz, H-5), 7.32 (1H, d, J = 2.6 Hz, H-3), 8.26 (1H, d, J = 6.0 Hz, H-6). Anal. Calcd for $C_6H_3NO_2$: C, 59.51; H, 2.50; N, 11.57. Found: C, 59.41; H, 2.37; N, 11.11.
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11. *General procedure for the preparation of pyridones **5**.* Amide **4** (0.14 mmol) was added to a solution of DMF-DMA (27 mg, 0.28 mmol) in toluene (2 mL). The reaction mixture was stirred in toluene under ambient conditions for 24 h, then the solvent was removed and the residue recrystallized from an appropriate solvent.
12. *N,1-Bis(4-methoxyphenyl)-4-oxo-6-(trifluoromethyl)-1,4-dihydropyridine-3-carboxamide (**5d**).* This compound was obtained from **4d** as a colorless solid, yield 35 mg (68%), mp 182–183 °C (EtOH). IR (ATR) 3080, 3000, 1679, 1611, 1578, 1508 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.74 (3H, s, MeO), 3.85 (3H, s, MeO), 6.94 (2H, d, J = 9.0 Hz, Ar), 7.12 (2H, d, J = 9.0 Hz, Ar), 7.20 (1H, s, H-5), 7.61 (2H, d, J = 9.0 Hz, Ar), 7.64 (2H, d, J = 9.0 Hz, Ar), 8.37 (1H, s, H-2), 12.00 (1H, s, NH); ^{19}F NMR (376.5 MHz, DMSO-d_6, C_6F_6) δ 101.9 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 55.6, 114.2, 114.4, 118.9, 119.3 (CF_3, q, $^1J_{C,F}$ = 275.0 Hz), 119.9 (q, $^3J_{C,F}$ = 4.2 Hz), 121.2, 128.8, 131.1, 132.7, 138.2 (q, $^2J_{C,F}$ = 33.5 Hz), 149.2, 155.8, 160.2, 160.4, 176.3. Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.10; N, 6.70. Found: C, 60.40; H, 4.28; N, 6.82. *N,1-Bis(4-methoxyphenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide (**5h**).* This compound was obtained from **4h** as a colorless solid, yield 29 mg (70%), mp 201–202 °C (PhMe). ^1H NMR (400 MHz, DMSO-d_6) δ 3.75 (3H, s, MeO), 3.84 (3H, s, MeO), 6.65 (1H, d, J = 7.4 Hz, H-5), 6.88 (2H, d, J = 8.9 Hz, Ar), 7.14 (2H, d, J = 8.9 Hz, Ar), 7.62 (4H, m, Ar), 8.17 (1H, dd, J = 8.9, 2.4 Hz, H-6), 8.62 (1H, d, J = 2.4 Hz, H-2), 12.50 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 55.6, 114.2, 115.0, 118.5, 119.9, 121.1, 124.8, 131.6, 135.9, 141.3, 143.9, 155.5, 159.4, 161.3, 176.7. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.70; H, 5.20; N, 8.02.
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